OFD I Syndrome and Mental Retardation

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In 1954, Papillon-Léage and Psaume (*20, 21*) described eight patients with similar congenital anomalies involving abnormalities of the oral frenula, digits, and dentition, clefts of the tongue, lip, and palate, mental retardation, hypoplastic nasal cartilages, and several other defects. Similar cases first appeared in the English literature in 1961 when Gorlin, Anderson, and Scott (*12*) presented four affected females in one family and a forme fruste in another. They attributed the mode of inheritance to a dominant pattern with lethality in males. The name oral-facial-digital syndrome, or OFD syndrome, was first used by Ruess, Pruzansky, Lis, and Patau (*25*) in their report of twelve cases. Recently, Rimoin and Edgerton (*23*) described a second type of oral-facial-digital syndrome. They suggested referring to the two types as OFD I and OFD II. The purpose of this paper is to review the syndrome and discuss the variable expressivity with regard to mental retardation.

Physical Characteristics

Many case reports have been published which describe in detail the physical characteristics of OFD I syndrome (*1, 5, 7, 13, 25, 26*). The most striking oral finding is the hypertrophied frenula which extend from the buccal mucosa to the alveolus. The frenula, often seen in both arches, form numerous fibrous bands which may actually create a cleft of the alveolar ridge (Figures 1 and 2). Hypertrophy of the lingual frenum may cause severe ankyloglossia. True clefts of the secondary palate are often seen. There may be a congenital absence of lateral incisors, especially where clefts are present (Figures 1 and 2). Supernumerary primary and/or permanent cuspids may be present (Figure 3). Enamel hypoplasia has been noted (*1, 5, 13, 25, 27*). Lateral palatal tori are often reported (*1, 7, 12, 13, 27*), but these may actually be pseudoclefts of the palate where there has been a failure of the lateral palatal shelves to fuse and the intervening area is covered only by soft tissue (Figure 3). A bifid, trifid, or multilobed tongue is commonly seen.

Frequently observed facial malformations include hypoplasia of the nasal cartilages, dystopia canthorum, discrepancy in size of the nostrils, milia of the ear pinnae, and varying degrees of hair loss. Another facial feature is a pseudocleft of the upper lip in the midline (Figure 4).

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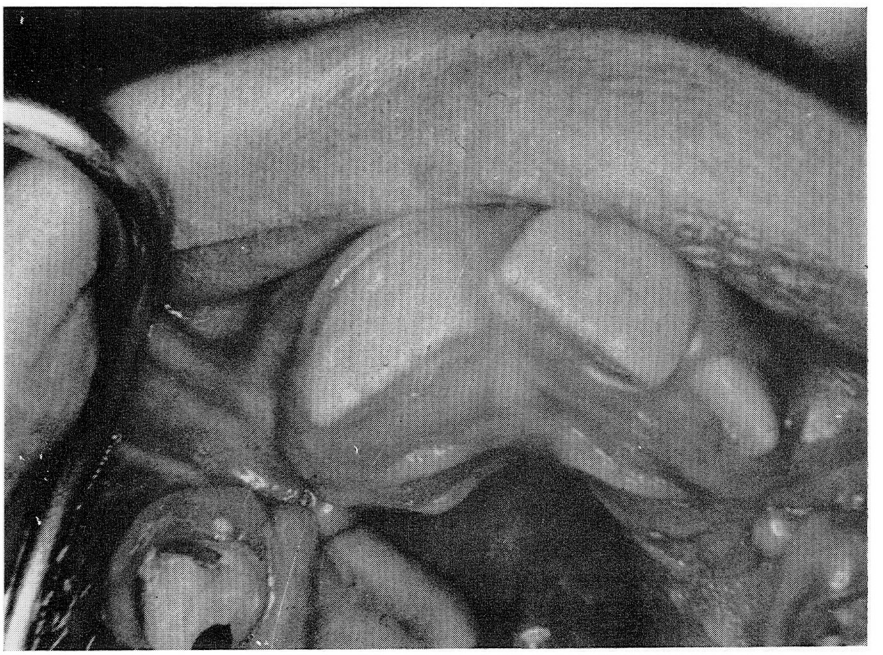

FIGURE 1. Hypertrophied frenula and cleft of the maxillary alveolus. The right lateral incisor is absent.

Digital anomalies include characteristic dermatoglyphic patterns (*4, 6*), brachydactyly, syndactyly, and clinodactyly. Hands are most often affected, but anomalies do occur on the feet.

Other defects associated with OFD I syndrome may include an increased incidence of mental retardation and central nervous system disorders, speech impairment, hearing loss, polycystic kidneys, and cutaneous dysplasia with decreased or absent sebaceous glands (*26*).

Mental Retardation

Mental retardation is not a consistant finding in patients with OFD I syndrome. The incidence of OFD I has been estimated at about 2 per 100,000 Caucasian births (*27*), and it has been estimated that thirty to fifty per cent of patients exhibiting this syndrome have a subnormal level of intelligence (*5, 12, 13, 21, 23, 25*). In general, the etiology of mental retardation is extremely complex, and a direct cause and effect relationship is difficult to establish. The methods of assessment of mental retardation in case reports of OFD I vary. Papillon-Léage and Psaume (*20, 21*) did not state the manner in which they judged half of their reported patients to be mentally retarded, nor did they state the degree of retardation. Gorlin et al (*12*) found that three of the four patients they reported were mentally retarded. Clinical observation was the only method of

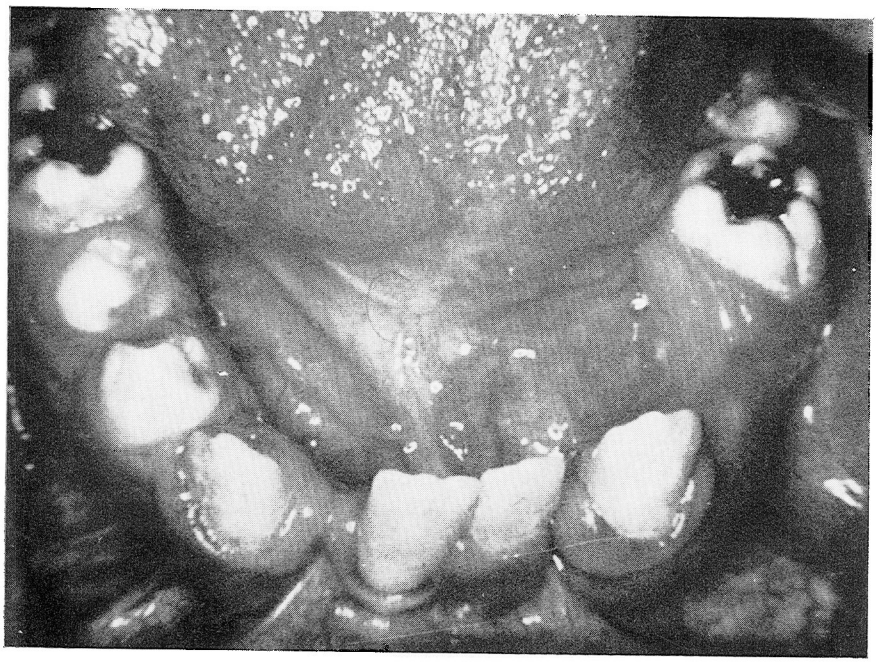

FIGURE 2. Hypertrophied frenula and cleft of the mandibular alveolus. Right and left lateral incisors are absent.

assessment in two of these patients because of a family unwillingness to participate in formal testing. The third affected patient had been institutionalized for twenty-one years and was classified as manic depressive, which should cast doubt on the reliability of any formal testing. Ruess et al (*25*) employed various standardized tests of intelligence for eight of the twelve cases reported. Four of these patients achieved scores consistent with a classification of average intelligence. The four patients with inferior performance on the tests presented with different etiologies contributory to mental retardation: 1) hydrancephaly, 2) hydrocephaly with porencephalic cyst, 3) primary mental retardation with speech and audiologic deficits and cultural deprivation, and 4) diffuse brain damage with cultural deprivation. Four other patients who were not tested were judged clinically to possess normal intelligence. Pruzansky, Ruess, and Buzdygan (*22*) judged a Negro girl with OFD I to be mentally deficient. Attempts made at formal testing of this girl at ages four and five were thwarted by her lack of cooperation. Their assessment of the patient's mental abilities was made on the basis of clinical observation, evaluation of isolated test item responses, and reported functional behavior in the home environment. Recently, Axrup et al (*1*) reported a five year old girl affected with OFD I to be mentally normal. Their assessment was based on the girl's performance on the Terman-Merrill intelligence test and a normal elec-

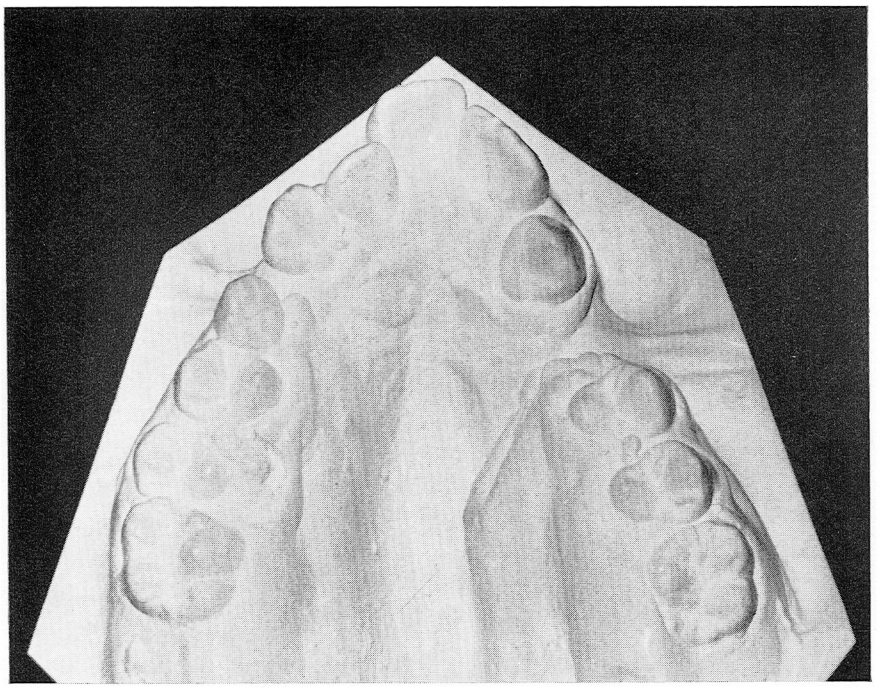

FIGURE 3. Plaster model showing lateral palatal shelf. Note the supernumerary right cuspid.

troencephalogram. Wahrman et al (*27*) reported mental retardation in a sixteen month old male with 47/XXY chromosomes (Klinefelter's syndrome) and OFD I syndrome. This patient was reported to have partial agenesis of the corpus callosum with a lipoma in the rostral portion of the corpus callosum. Doege and co-workers (*6*) made the first attempt at a controlled study of mental retardation in OFD I syndrome. They endeavored to eliminate the effect of culture and environment by comparing affected and non-affected sisters in two generations of a large family with seventeen OFD I females. In addition, they compared another OFD I female from this same family and her non-affected first cousin. The paired sisters were consecutive in birth order and were of the same parental origin. Formal testing of the affected mother indicated that she possessed normal intelligence. The results of their study indicate that all affected offspring who were tested were mentally retarded, ranging from borderline to profound; however, two non-affected offspring were also classified as being mentally retarded on the basis of their test scores. It was suggested that there may be a direct relationship between the level of intelligence and the severity of OFD I anomalies. There is some indication from this study that OFD I females tend to score lower on tests of verbal skills while showing higher scores in performance areas.

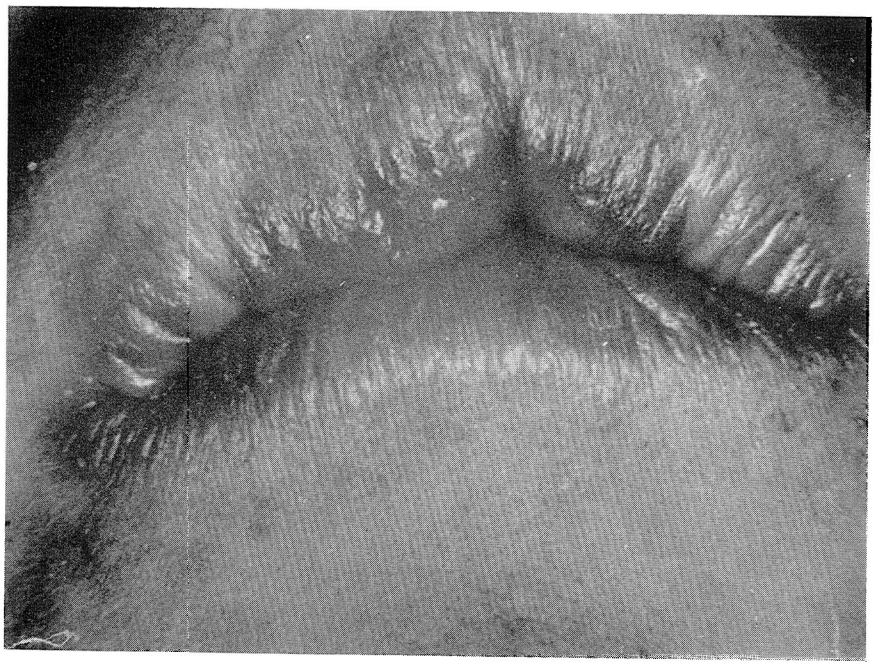

FIGURE 4. Midline pseudocleft of the upper lip.

With tests of intelligence relying more and more on verbal skills, one might consider the interaction between hearing loss, speech impairment, cleft palate, and mental retardation in OFD I patients. There may be an increased incidence of hearing loss, speech impairment and intellectual impairment in cleft palate poulations (*8, 10, 16*), and there is a high incidence of cleft palate in OFD I populations.

Gorlin (*11*) states, "The intelligence quotient in these individuals is somewhere around 70." The evidence does, in fact, indicate a high incidence of mental retardation in OFD I patients, but retardation is by no means a cardinal feature of the syndrome. Until more is known about the multifactorial etiology of mental retardation in general, broad, all-encompassing statements about the mentality of OFD I patients should be avoided.

Although substantive data is scanty, clinical observations by experienced professionals cannot be discounted in assessing relative levels of mental function. When a patient presents with OFD I syndrome, every effort must be made to evaluate her mental abilities on an individual basis in order to maximize her potential for adapting to society. Ruess, Pruzansky and Lis (*24*) have emphasized the need to analyze critically the developmental, environmental, and situational factors of each OFD I patient individually. In this way, the highest degree of success may be attained in the long range planning for the habilitation of these patients.

Ruess et al. have stressed that a normal level of intelligence is seen in many patients with OFD I syndrome.

Genetics

It has been suggested that OFD I is transmitted as an X-linked dominant trait with lethality in homozygous males (*6, 11, 19, 27*). One exception to this pattern was reported in 1967 where OFD I syndrome appeared in a chromosomally normal male (*17*). Prior to the recognition of OFD II syndrome, there were two reports in the English literature of OFD in males (*15, 27*). One of these males, however, appears to have OFD II syndrome with bilateral polysyndactyly of the large toe. Cytogenetic studies of the other male revealed 47/XXY chromosomes. The presence of the X chromosomes may serve to explain the viability of this male with OFD I syndrome. There have been other reportes of OFD I in males (*2, 3, 18*), however, close evaluation of the physical findings would indicate that the diagnosis of OFD I syndrome may be open to discussion.

In a dominant pattern with lethality in males, a theoretical sex ratio of 2:1, female to male, would be expected. Analysis of OFD I pedigrees indicates that this ratio is closely approximated (*6*).

From the viewpoint of genetic counseling, an affected female has a fifty per cent chance of passing the trait to her daughters. Any sons that survive will not be affected. It should be stressed that a non-affected female offspring is not likely to pass the trait to her daughters. A non-affected female offspring has the same probability of having an affected daughter as does a non-affected female in a normal population. A high incidence of abortions and stillbirths may be seen in an affected family. Although the greatest majority of OFD I patients appears to inherit the trait in an X-linked dominant pattern with lethality in males, the possibility of other modes of transmission or new mutation should not be overlooked (*17*).

In 1967, Rimoin and Edgerton (*23*) presented evidence to indicate the existence of a second type of oral-facial-digital syndrome. It was referred to as OFD II, or Mohr syndrome. Anomalies of the tongue, lip, palate, frenula, and digits are similar in both syndromes; however, there are distinct differences which serve to distinguish the two. Bilateral polysyndactyly of the large toe is the most consistent characteristic finding in patients with OFD II. This bilateral feature has not been reported in patients with OFD I. Although hypertrophied frenula are seen in both syndromes, these are not associated with clefts of the alveolar ridges in OFD II, and the distribution is often limited to the midline. The lack of clefting of the alveolus may account for the fact that the dentition in OFD II is more often normal in number. Hair and skin defects have not been noted in OFD II, and mental retardation is apparently not a common feature.

OFD II may occur in either males or females and appears to be trans-

mitted as an autosomal recessive trait. The pedigree presented by Rimoin and Edgerton showed affected siblings of both sexes with apparently normal parents. They also cited another study of a similarly affected male where a history of consanguinity was revealed.

Every effort should be made to distinguish OFD I from OFD II because of the implications in genetic counseling. A patient with OFD II whose mate is not similarly affected will not transmit the trait; however, all offspring will be carriers.

Summary

Although a high incidence of mental retardation is seen in OFD I populations, it is stressed that the syndrome is not incompatible with normal intelligence. Each patient's mental abilities should be assessed individually. Effective long range planning of the education and training of these patients will permit adaptation to the demands of society. Clinical manifestations of the syndrome include hypertrophied frenula, clefts of the palate, alveolus, lip, and tongue, hypoplastic nasal cartilages, brachydactyly, and syndactyly. OFD I appears to be transmitted as an X-linked dominant trait with lethality in the hemizygous male. OFD II appears to be transmitted as an autosomal recessive trait. There are other distinct differences between OFD I and OFD II. Differentiation between these two syndromes is important because of the implications in genetic counseling.

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